REMARKS

Applicants respectfully request continued examination in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 26-29, 32-34, 63, and 65-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stephenson et al. (BMC Molecular Biology, 12/21/2001, 2(15):1-9) in view of Flanagan et al. (WO 96/26958) and Genentech (WO 00/30673). Applicants respectfully traverse the rejection.

Independent claim 26 recites "an isolated monoclonal antibody which binds to an extracellular domain of an EphB4 protein and promotes apoptosis in a tumor cell, wherein the antibody is selected from bispecific, single-chain, chimeric, human, and humanized antibodies." Applicants emphasize that the claimed EphB4 antibody is clearly defined by its ability to promote apoptosis in a tumor cell.

Applicants submit that the Office has not satisfied the requirement of establishing a *prima facie* case of obviousness. The Office concedes that Stephenson et al. do **not** teach: "a monoclonal antibody which promotes apoptosis in a tumor cell." See Office Action, first full paragraph on page 8. However, the Office Action asserts that the deficiencies are made up in the teachings of Flanagan et al. and Genentech, and that one of skill in the art would recognize that the antibodies taught by the combined teachings would inhibit clustering of EphB4 and promote apoptosis. To reach this conclusion the Office Action relies on Xia et al. (Clinical Caner Research, June 2005, 11(12): 4305-4315) for evidence that EphB4 normally phosphorylates proteins such as Akt that are known to promote tumor cell survival. From this, the Office concludes that agents, like EphB4-binding antibodies, that inhibit EphB4 signaling inherently induce apoptosis.

First, Applicants submit that the antibody used in Stephenson et al. does not promote apoptosis and that Flanagan et al. and Genentech fail to bridge the gap between the claimed invention and Stephenson et al. because neither Flanagan et al. nor Genentech teach antibodies that

bind to EphB4 and promote apoptosis. To the contrary, Stephenson et al. disclose a polyclonal EphB4 antibody (H-200) that has affirmatively been shown to not induce apoptosis in a tumor cell. Queen Elizabeth Hospital (WO 2004/024773), an application that names Sally-Anne Stephenson as the inventor, discloses on page 28 that the H-200 antibody triggers cell death but "that cell death was not *via* apoptosis (Figure 6)." Therefore, Queen Elizabeth Hospital and Stephenson et al. teach away from EphB4 antibodies that promote apoptosis because the H-200 antibody does not induce apoptosis.

Second, Applicants submit that Xia et al. does not support the proposition that antibodies that bind to the extracellular domain of EphB4 must necessarily promote apoptosis. Xia et al. shows that siRNA mediated knock-down of the EphB4 protein triggers apoptosis and results in a reduction in Akt phosphorylation. However, siRNA-mediated knock-down of EphB4 protein production is **not** biologically equivalent to an antibody binding to the extracellular domain of EphB4. And just because siRNA mediated knock-down of EphB4 results in a reduction in Akt phosphorylation it does not follow, *a priori*, that EphB4-binding antibodies must necessarily induce apoptosis. The flaw in the reasoning upon which the rejection is based is actually revealed in Xia et al. Under the Office Action's interpretation of Xia et al., any inhibition of EphB4 signaling should trigger apoptosis. But this is not the case. For example, Xia et al. disclose that siRNA-mediated knock-down of EphB4's ligand Ephrin B2 – which would also inhibit EphB4 signaling – does not trigger apoptosis. Therefore, even assuming *arguendo* that all EphB4-binding antibodies inhibit EphB4 signaling, it does not follow that all EphB4-binding antibodies must necessarily induce apoptosis.

Third, the Office's finding of obviousness relies on the notion that EphB4-binding antibodies inherently trigger apoptosis. As described above, Applicants respectfully submit that the Office Action provides no evidence that the induction of apoptosis is an inherent feature of EphB4-binding antibodies. Further, the disclosure of Queen Elizabeth Hospital and the disclosure of Krasnoperov et al. (WO 2005/090406) amply demonstrate that EphB4-binding and apoptosis can occur independently, and one does not follow from the other. As described above, Queen Elizabeth Hospital discloses an EphB4-binding antibody (H-200) that does not induce apoptosis. Similarly, Krasnoperov et al. disclose in Table 1 on page 36, an EphB4-binding monoclonal antibody (Ab. No.

1) that does not induce apoptosis. Therefore, antibodies that bind EphB4 do not necessarily induce apoptosis, and a rejection based on inherency cannot stand.

Accordingly, the combination of Stephenson et al., Flanagan et al., and Genentech fails to teach all elements of independent claim 26, such as a monoclonal antibody against EphB4 that promotes apoptosis in a tumor cell.

In view of the above, Applicants submit that independent claim 26 is non-obvious over the cited references. Even if the cited references were combined, the combination still fails to teach each and every limitation of independent claim 26. For the same reasons, all claims depending from claim 26 are *a fortiori* patentably non-obvious over these cited references. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 26-29, 32-34, 63, and 64-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stephenson et al. (BMC Molecular Biology, 12/21/2001, 2(15):1-9) in view of Flanagan et al. (WO 96/26958) and Genentech (WO 00/30673), and further in view of Sola et al. (Journal of Virology, May 1998, 3762-3772). Applicants respectfully traverse the rejection.

This rejection seems to be directed to dependent claim 64 only. Specifically, the Office Action asserts that "[t]he combined teachings of Stephenson et al, Flanagan et al, and Genentech do not specifically teach a non-human transgenic animal expressing the antibody of claim 26. However, this deficiency is made up in the teachings of Sola et al. Sola et al teaches producing recombinant monoclonal antibodies in mice (see pages 3767-3768, in particular)." Office Action, page 9, lines 3-7.

Applicants respectfully disagree. As described above, independent claim 26 is not obvious over the combination of Stephenson et al., Flanagan et al. and Genentech. Since claim 64 depends from claim 26 and recites the limitations of claim 26, claim 64 is *a fortiori* patentably non-obvious over these cited references. The deficiency of these cited references is not made up by the other cited reference (Sola et al.).

In sum, Applicants submit that all of the pending claims are non-obvious over the cited references. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

CONCLUSION

For the foregoing reasons, Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. The Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. **VASG-P01-002**.

Dated: March 19, 2010

Respectfully submitted,

By_/Andrew W. Shyjan/_
Andrew W. Shyjan, Ph.D., J.D.
Registration No.: 61,294
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys for Applicant